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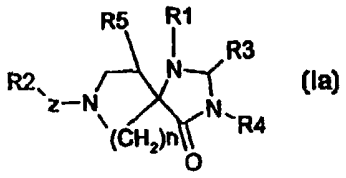
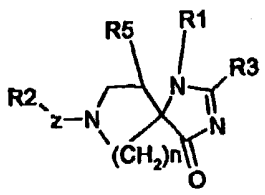


(Ia)



(Ib)

(57) Abstract

The present invention relates to use of small organic compounds acting as opioid receptor ligands for the treatment of vasomotor disturbances. In particular the present invention relates to the triazaspiro compounds of general formula (Ia) or (Ib) wherein R^1 is selected among phenyl, arylalkyl or thienyl; R^2 is selected among aminophenyl, C_{1-6}–monoalkylaminophenyl, C_{1-6}–dialkylaminophenyl, cyanophenyl, C_{2-6}–alkylphenyl, naphthyl, tetrahydronaphthyl, furanyl, indanyl, benzothienyl or benzofuranyl; R^3 is hydrogen, C_{1-6}–alkyl, phenyl, benzyl, or acetyl; R^4 is hydrogen or $(CH_2)_m$–(CHR^9)–$(CH_2)p$–AR^{11}; R^5 is hydrogen or C_{1-4}–alkyl; z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}–alkyl, phenyl or arylalkyl – or z is C_{2-8}–alkylene, C_{2-8}–alkenylene or C_{2-8}–alkynylene; n is 1 or 2; or a pharmaceutically acceptable salt thereof for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

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TITLE

Novel 1,3,8-triazaspiro[4.5]decanones with high affinity for opioid receptor subtypes

FIELD OF INVENTION

The present invention relates to use of small organic compounds acting as opioid receptor ligands for the treatment of vasomotor disturbances. In particular the present invention relates to the compounds of the general formula Ia or Ib for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THE INVENTION

A "hot flush" is a sudden transient sensation ranging from warmth to intense heat and typically accompanied by flushing and perspiration. It is the classic sign of the menopause and the predominant complaint of menopausal women.

A positive correlation between plasma levels of calcitonin gene-related peptide (CGRP) and frequency of hot flushes in women has recently been reported (Chen et al., 1993, Lancet (342) 49), in accordance with the potent vasodilatory effect of CGRP (Brain et al., 1985, Nature, (313) 54-56).

Also, a positive correlation between CGRP antagonists and diabetes, septic shock and inflammation has been described (Feurstein, G, Willette, R and Aiyar, N., 1995, Can. J. Physiol. Pharmacol. 73: 1070-1074).

Recently, a novel heptadecapeptide, nociceptin, was discovered (Meunier et al., 1995, Nature (377) 532-535, Reinscheid et al., 1995, Science (270) 792-794).

Nociceptin and analogues thereof have been disclosed in WO 97/07212 , EP 813065 and in WO 97/07208. These peptides and inhibitors thereof are said to be useful for antagonising physiologic effects of an opioid in an animal, and for treating/preventing a disease related to: hyperalgesia, neuroendocrine secretion, stress, locomotor activity, anxiety etc.

Jenck, F et. al. also found, that Orphanin FQ acts as an anxiolytic to attenuate behavioralresponses to stress (PNAS Vol. 94, 1997).

It is well known that triaza-spiro compounds are vasodilating agents and morphine-like analgesics as disclosed in US 3,238,216 and US 3,155,670 by Janssen.

SUMMARY OF THE INVENTION

It has been found that members of a novel group of triaza-spiro compounds have high affinity for nociceptin receptors which make them useful as regulators of peripheral vasomotor effects known as hot flushes.

The present invention provides a compound of the formula Ia or Ib as disclosed below or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of Type II diabetes, septic shock, inflammation, incontinence and vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

Further objects will become apparent from the following description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to use of a small organic compound acting as an opioid receptor ligand for the preparation of a pharmaceutical composition for the treatment of a disease selected from migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence, vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes and/or for alleviating symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

In another aspect the invention relates to use of a small organic compound acting as a Nociceptin receptor ligands with a molecular weight of less than 1000 or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

In still another aspect the invention relates to use of small organic compounds acting as Nociceptin receptor ligand with a molecular weight less than 600 or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

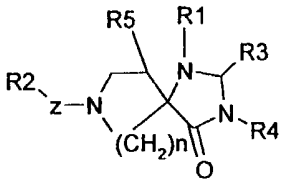
In yet another aspect the invention relates to use of a small organic compound acting as a Nociceptin receptor ligand with less than 5 amide bonds or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

In a further aspect the invention relates to use of a small organic compound acting as a Nociceptin receptor ligands wherein said compound has no amide bonds or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

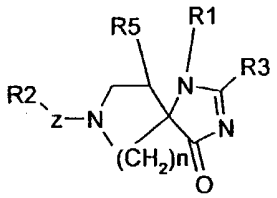
In still another aspect the invention relates to use of a compound wherein said compound comprises a triaza-spiro compound acting as a Nociceptin receptor ligand or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

In yet another aspect the invention relates to use of a small organic compound acting as a Nociceptin receptor ligand with an IC_{50} less than 1μM or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

In a second aspect the invention relates to a compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogene, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is

aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$ where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

n is 1 or 2

or a pharmaceutically acceptable salt thereof.

In another aspect of the invention R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogene, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl.

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, furanyl, indanyl, benzothienyl, benzofuranyl, said groups may be substituted with one or more of halogene, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl , or C_{1-6}-alkoxy

or R^2 is phenyl provided that R^1 is not phenyl, R^3 is not methyl or hydrogen and R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl.

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl.

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$ where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group.

R^5 is hydrogen or C_{1-4}-alkyl.

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene.

n is 1 or 2

or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention R^1 is C_{1-6}-alkyl, phenyl, arylalkyl or thienyl.

In yet another embodiment of the invention R^2 is

aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, furanyl, indanyl, benzothienyl, benzofuranyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, - $NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, or C_{1-6}-alkoxy.

In still another embodiment of the invention R^2 is
cyanophenyl or naphthyl, said groups may be substituted with one or more of fluorine, chlorine, bromine, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$ wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl.

In a preferred embodiment of the invention n is 2.

Another preferred embodiment of the invention comprises compound Ia wherein R^1, R^2, R^3, R^4, R^5 , z and n are defined as above.

In still another preferred embodiment of the invention
R^1 is phenyl;

In yet another preferred embodiment of the the invention the compounds are selected from the following:

(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester, **(1a)**
{8-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester, **(1b)**
[8-(3-Cyano-3,3-diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1c)**

[8-(4-Nitro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1d)**

[4-Oxo-1-phenyl-8-(3-phenyl-propyl)-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1e)**

[4-Oxo-8-(3-phenoxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1f)**

[4-Oxo-8-(4-phenoxy-butyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1g)**

[8-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1h)**

{8-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester, **(1i)**

(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester, **(1j)**

{8-[2-(4-Fluoro-phenoxy)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester, **(1k)**

[8-(6,7-Dimethoxy-2-oxo-2H-chromen-4-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1l)**

[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1m)**

[8-(3-Cyano-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1n)**

3-(3-Methoxycarbonylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-benzoic acid methyl ester, **(1o)**

[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1p)**

[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester, **(1q)**

(8-Anthracen-9-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester ,**(1r)**

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]pentanoic acid methylester,

N-(2-Guanidino-ethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

3-(7-Amino-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

3-(1H-Imidazol-4-yl)-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

5-Guanidino-2-(R)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

N-(3-Guanidino-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

3-(5-Amino-pentyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

N-(3-Amino-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

N-(2-Amino-ethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

N-[7-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-heptyl]-guanidine,

3-Ethyl-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-N-(tetrahydro-furan-2-ylmethyl)acetamide,

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-N-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-acetamide,

6-Amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoic acid amide,

N-Carbamoylmethyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-phenyl-acetamide,

6-Amino-2-(S)-(2-{6-amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoylamino}-acetylamino)-hexanoic acid amide,

5-Guanidino-2-(S)-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-pentanoic acid amide or

5-Guanidino-2-(S)-(2-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-acetylamino)-pentanoic acid amide.

In a most preferred embodiment of the the invention the compounds are selected from the following:

(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,

[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

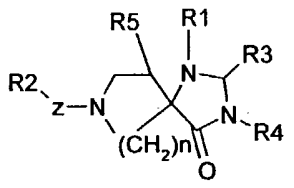
[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

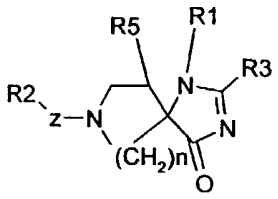
5-Guanidino-2-(R)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide or

3-(7-Amino-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

In a third aspect the invention comprises use of a compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is

phenyl, phenoxy, benzodioxinyl, cyanodiphenylmethyl, aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$

where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group; or

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

n is 1 or 2

or a pharmaceutically acceptable salt thereof for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

In another embodiment of the invention the composition is in a form suitable for oral, nasal, transdermal, pulmonal, or parenteral administration.

In a further embodiment of the present invention the compound of the formula Ia or Ib is administered as a dose in the range from about 0.01 to about 5000 mg per patient per day, preferably from about 1 to about 1000 mg per patient per day, especially from about 10 to about 100 mg per patient per day, e.g. about 100 mg per patient per day.

In a fourth aspect the invention relates to a method for the treatment or prevention of migraine, Type II diabetes, sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects

known as hot flushes or hot flashes, the method comprising administering to a patient in need thereof an effective amount of compound of the formula Ia or Ib or a pharmaceutically acceptable salt thereof.

In a fifth aspect the invention relates to a pharmaceutical composition comprising triaza-spiro compounds with high affinity to the nociceptin receptor, or a pharmaceutically acceptable salt thereof.

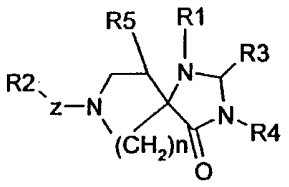
In a sixth aspect the invention relates to a method of treatment symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

The effective, such as the therapeutically effective amount of a compound of the formula Ia or Ib will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

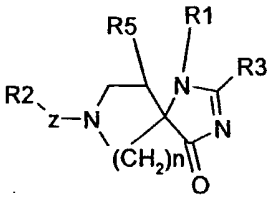
As used herein the term "patient" comprises any mammal which may benefit from treatment or prevention of vasomotor disturbances, such as a human, especially if the mammal is a female, such as a woman. However, "patient" is not intended to be limited to a woman.

As used herein the term " small organic compounds" refers to compounds with a molecular weight below 1000 and with less than 5 amide bonds or no amide bonds.

As used herein the term "triaza-spiro" represents a compound of formula



or



with various substituents as defined above.

As used herein the term "high affinity" represents an IC_{50} below 1μM.

As used herein the term "arylalkyl" refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic hydrocarbon; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

As used herein the term "C_{1-6}-alkyl" represent a branched or straight alkyl group or cycloalkyl with five or six carbon in the ring. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl and the like.

As used herein the term "C_{1-6}-alkoxy" alone or in combination is intended to include those C_{1-6}-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked thorugh an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

As used herein the term "halogen" means fluorine, chlorine, bromine or iodine.

As used herein the term "amino acid residue or peptidyl residues" is also meant to comprise naturally occurring or synthetically produced amino acids linked to the compound by an amide bond.

As used herein the terms "C_{2-8}-alkylene" represent a branched or straight alkyl group having from one to the specified number of carbon atoms. Typical C_{2-8}-alkylene groups include, but are not limited to, ethylene, n-propylene, iso-propylene, butylene, iso-butylene, sec-butylene, tert-butylene, pentylene, iso-pentylene, hexylene, iso-hexylene and the like.

As used herein the terms "C_{2-8}-alkenylene" represents an olefinically unsaturated branched or straight group with at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenylene, allylene, iso-propenylene, 1,3-butadienylene, 1-butenylene, hexenylene, pentenylene, and the like.

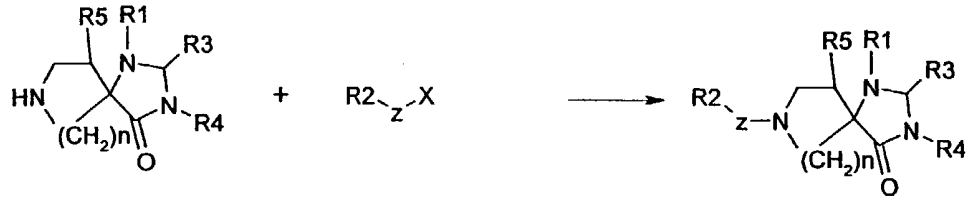
As used herein the terms "C_{2-8}-alkynylene" represent an unsaturated branched or straight group having at least one triple bond. Examples of such groups include, but are not limited to, 1-propynylene, 1-butynylene, 2-butynylene, 1-pentynylene, 2-pentynylene and the like.

As used herein the term "ligand" is also meant to comprise a compound with agonistic, partial agonistic or antagonistic activity specifically binding to receptor proteins.

As used herein the term "treatment" is also meant to comprise prophylactic treatment.

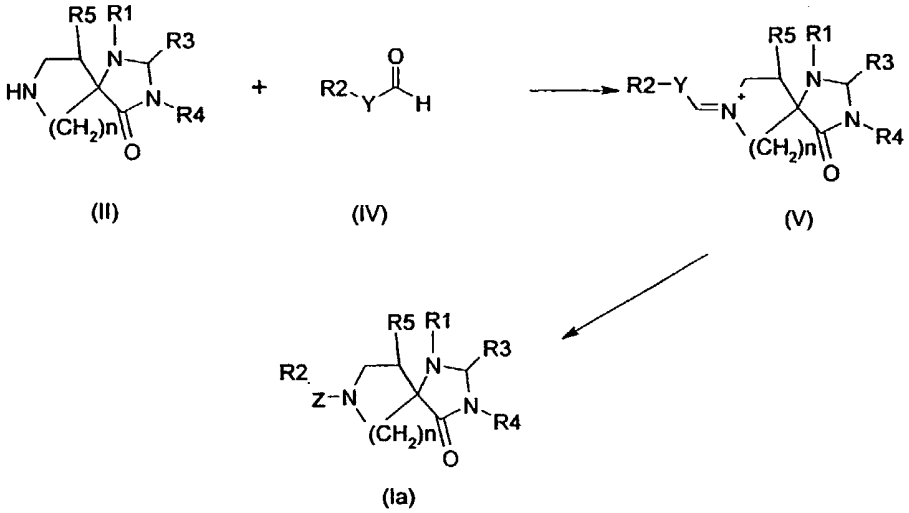
The preparation of compounds of formula Ia may include, but are not limited to the following methods:

A:



A compound of formula (II) wherein R^1, R^3, R^4, R^5 and n are as defined above may be allowed to react with a compound of formula (III), wherein R^2 and z are defined as above and X is a suitable leaving group such as halogen, p-toluene sulphonate or mesylate. This alkylation reaction may be carried out in a solvent such as acetone, dibutylether, 2-butanone, methyl ethyl ketone, ethyl acetate, tetrahydrofuran (THF) or toluene in the presence of a base e.g. sodium hydride and a catalyst, e.g. an alkali metal iodide at a temperature up to reflux temperature for the solvent used for e.g. 1 to 120 h. Compounds of formula (II) may be prepared by known methods, e.g. as described in US-Patent 3,238,216. Compounds of formula (III) are commercially available or may readily be prepared by methods familiar to those skilled in the art.

B:



(II) (IV) (V)

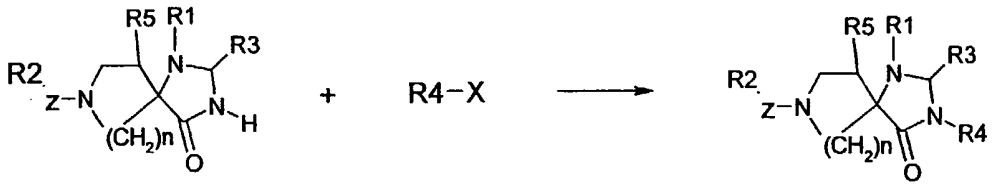
(Ia)

A compound of formula (II) wherein R^1, R^3, R^4, R^5, and n are as defined above may be allowed to react with an aldehyde of formula (IV), wherein R^2 is as defined above and the linker y is one C-atom shorter than linker z, where z is as defined above, to form an imine of formula (V). The reaction may be carried out in a suitable solvent like a lower aliphatic alcohol as e.g. ethanol or an ether as e.g. tetrahydrofuran or a mixture of these. In a second step, the formed iminium derivative of formula (V) is then reduced to an amine of formula (Ia) by the addition of a suitable reducing agent, e.g. a hydride as sodium cyanoborohydride or sodium borohydride in e.g. 1 to 120 h at 20° C to reflux temperature.

Compounds of formula (Ia) may also be prepared in a parallel fashion using solid phase technology, e.g. as described by F. Zaragoza and S.V. Petersen, Tetrahedron, 52, 10823 (1996). In this case, R^4 in a compound of formula (II) is replaced by $(CH_2)_m$-(CHR^9)-$(CH_2)_p$-$C(O)R^{7b}$, wherein m, p and R^9 are as defined above and R^{7b} is a resin-O- or a resin-NH-residue.

The above described reactions are followed by a cleavage from the resin to form a compound of formula (Ia). The Cleavage conditions used depend on the type of resin used and are commonly known to those skilled in the art.

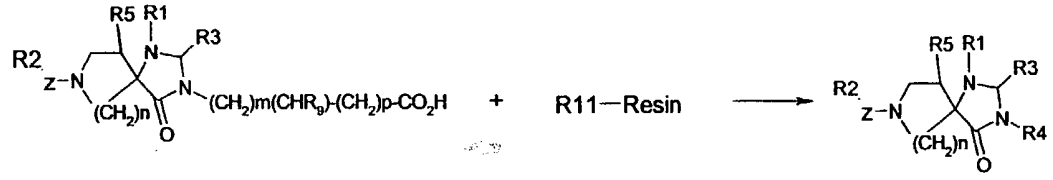
C:



(VI) (VII) (Ia)

A compound of formula (VI) wherein R^1, R^2, R^3, R^5, z and n are as defined above, may be deprotonated at N3 with a suitable base, as sodium hydride, n-butyl lithium or potassium tert.-butoxide in an aprotic solvent as e.g. dimethyl formamide or dimethylsulfoxide and subsequently allowed to react with a reagent of formula (VII), wherein R^4 and X are as defined above. The reaction may be carried out at temperatures from 0 °C to reflux temperature, preferably at room temperature in 1 to 24 hours, to form a compound of formula (Ia).

D:



(VIII) (IX) (Ia)

A compound of formula (Ia) may further be synthesized by allowing a compound of formula (VIII), wherein R^1, R^2, R^3, R^5, R^9, m, p, n an z are as described above, to react with a compound of formula (IX), in which the R^{11} group bears a residue which is coupled to a resin and may be subsequently cleaved from the resin as an ester or amide moiety. The coupling reaction between (VIII) and (IX) may be carried out in a suitable solvent as e.g. dimethyl formamide or N-methyl pyrrolidone using e.g. a coupling reagent from the class of the carbodiimides, a benzotriazol and an optional base as a hindered tertiary amine. These amide couplings are well documented in the literature and commonly known. Compounds of formula (IX)

may be commercially available resins, or can be prepared from such commercially available resins using general alkylation, reductive amination, or acylation methods.

Within the present invention, the compound of the formula Ia or Ib may be prepared in the form of pharmaceutically acceptable salts such as base or acid addition salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, maleic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compound of the formula Ia or Ib are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the formula Ia or Ib of this invention may form solvates with standard low molecular weight solvents using methods known to a person skilled in the art.

The compound of the formula Ia or Ib may be administered in pharmaceutically acceptable acid addition salt form . Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

A pharmaceutical composition for use in accordance with the present invention comprises, one or more compound of the formula Ia or Ib as active ingredient(s), or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing compounds of the formula Ia or Ib of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include Compound of formula Ia or Ib or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil,

gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatine, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula Ia or Ib dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

Any novel feature or combination of features described herein is considered essential to this invention.

Pharmacological effects:

Male Sprague Dawley rats (300±25 g) were anaesthetized with pentobarbital sodium (50 mg/kg i.p.) and polyethylene catheters were positioned in both femoral veins for the intravenous administration of drugs, such as nociceptin and analogues, and into the left femoral artery in order to measure arterial blood pressure and heart rate. The trachea was cannulated with polyethylene tubing and the rat was pithed, ventilated and drug treated as described by Nuki Y. et al. (Effects of Dorsal Rhizotomy on Depressor Response to Spinal Cord Stimulation Mediated by Endogenous Calcitonin Gene-related Peptide in the Pithed Rat. J. Neurosurg. 1993; 79:899-904).

Examples:

The process for preparing compounds of formula Ia or Ib and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

Hereinafter, TLC is thin layer chromatography, $CDCl_3$ is deuterio chloroform and DMSO-d_6 is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^1H NMR shifts (δ_H) are given in parts per million (ppm).

HPLC-MS analyses were performed on a PE Sciex API 100 LC/MS System using Method 1: a WatersTM 3 mm x 150 mm 3.5 µ C-18 Symmetry column and positive ionspray with a flow rate of 20 µL/minute. The column was eluted with a

linear gradient of 5-90% A, 85-0% B and 10% C in 15 minutes at a flow rate of 1 ml/min (solvent A = acetonitrile, solvent B = water and solvent C = 0.1% trifluoroacetic acid in water).

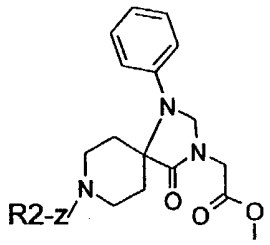
Method 2: a YMC ODS-A 120 Å s - 5μ 3 mm x 50 mm column and positive ionspray with a flow rate of 20 μL/minute. The column was eluted with a linear gradient of 5-90% A, 85-0% B and 10% C in 7.5 minutes at a flow rate of 1.5 ml/min.(solvent A = acetonitrile, solvent B = water and solvent C = 0.5% trifluoroacetic acid in water).

M.p. is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. (1978), 43, 2923-2925 on Merck silica gel 60 (Art. 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

EXAMPLE 1

8-Alkylated 4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl esters

(Method A)



Wang resin (2.17 g, 2.0 mmol) was placed in a solid synthesis flask equipped with a glass frit and swelled in dry dimethylformamide (15 ml) for 15 minutes. The excess solvent was removed by suction and a solution of Fmoc-3-carboxymethyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (2.05 g, 4.0 mmol) in dimethylformamide (8.0 ml) was added. The mixture was agitated for 5 minutes, dry pyridine (0.53 ml)

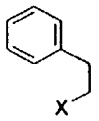
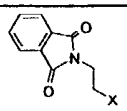
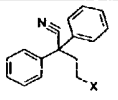
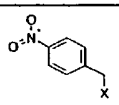
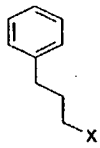
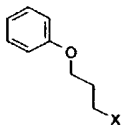
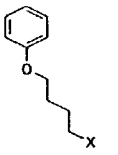
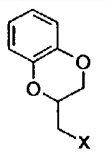
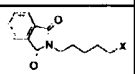
and 2,6-dichlorobenzoyl chloride (0.54 ml, 4.0 mmol) was added and the mixture was agitated for 20 h. The solution was removed by suction and the resin was washed with dimethylformamide (2x 10 ml) and 1,2-dichloroethane (4x 10 ml). Dichloromethane (8 ml), pyridine (0.81 ml, 10 mmol) and benzoyl chloride (0.81 ml, 7.0 mmol) were added to the resin and the mixture was agitated for 2 h. The solution was removed by suction and the resin was washed with dichloroethane (4x 10 ml), methanol (2x 10 ml) and N,N-dimethylformamide (2x 10 ml).

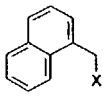
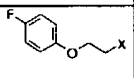
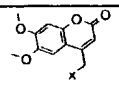
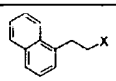
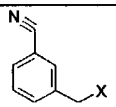
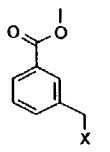
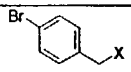
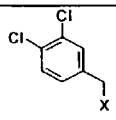
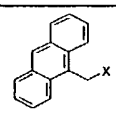
To remove the Fmoc group, the resin was agitated with 20% piperidine in N,N-dimethylformamide (10 ml) for 30 minutes. The solution was removed by suction, the resin was washed with N,N-dimethylformamide (2x 10 ml), dichloromethane (4x 10 ml) and methanol (3x 10 ml) and dried. This yielded the Wang resin (2.53 g) with attached 3-carboxy-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (0.67 mmol/g).

The following solid phase syntheses were carried out parallely using the apparatus described by F. Zaragoza and S.V. Petersen, Tetrahedron, 52, 10823 (1996).

Equal portions of the above resin (67 mg, 0.045 mmol) were placed in Teflon tubes equipped with a frit on a mechanical shaker. Dimethyl sulfoxide (1 ml), the appropriate alkyl bromide R^2-z-x (0.225 mmol) and diisopropylethylamine (0.029 g, 0.225 mmol) were added to the resin. The tubes were heated to 60 °C and agitated for 16 h. The resin was drained, washed with dimethyl sulfoxide (2x 1 ml), dichloromethane (4x 1 ml) and methanol (2x 1 ml).

A solution of sodium methoxide (0.009 mmol) in a mixture of tetrahydrofuran/methanol 4:1 (2 ml) was added to the resin and the suspension was agitated at 50 °C for 16 h. The mixture was neutralized by addition of a solution of acetic acid (0.01 mmol) in a mixture of tetrahydrofuran/methanol 4:1 (1 ml), the solution was drained and the resin was washed with tetrahydrofuran (1 ml). The combined filtrates were concentrated in vacuo to yield the title compounds.

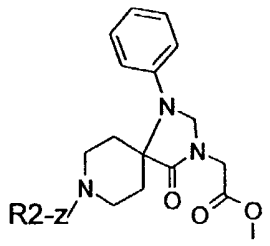
Entry	Name	R^2-z-X	MW calculated	LC/MS MH^+ rt [min] (method)	
1a	(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester		407.5	408.2	9.18 (1)
1b	{8-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester		476.5	477.2	8.90 (1)
1c	[8-(3-Cyano-3,3-diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		522.7	523.0	11.03 (1)
1d	[8-(4-Nitro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		438.5	439.2	9.43 (1)
1e	[4-Oxo-1-phenyl-8-(3-phenyl-propyl)-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		421.5	422.2	9.77 (1)
1f	[4-Oxo-8-(3-phenoxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		437.5	438.2	9.85 (1)
1g	[4-Oxo-8-(4-phenoxy-butyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		451.6	452.2	10.02 (1)
1h	[8-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		451.5	452.2	9.52 (1)
1i	{8-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-4-oxo-1-		518.6	519.2	9.68 (1)

	phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester				
1j	(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester		443.6	444.0	9.80 (1)
1k	{8-[2-(4-Fluoro-phenoxy)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester		441.5	442.0	9.68 (1)
1l	[8-(6,7-Dimethoxy-2-oxo-2H-chromen-4-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		521.6	522.0	8.90 (1)
1m	[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		457.6	458.2	10.40 (1)
1n	[8-(3-Cyano-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		418.5	419.2	9.10 (1)
1o	3-(3-Methoxycarbonylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-benzoic acid methyl ester		451.5	452.4	9.48 (1)
1p	[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		472.4	472.2	10.00 (1)
1q	[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		462.4	462.2	10.47 (1)
1r	(8-Anthracen-9-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester		493.6	494.2	11.22 (1)

EXAMPLE 2

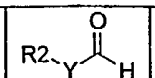
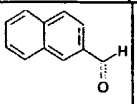
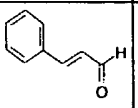
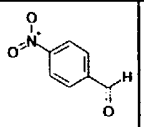
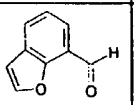
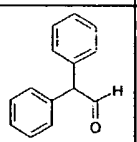
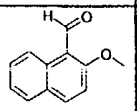
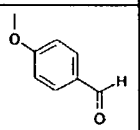
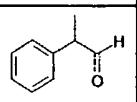
8-alkylated 4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl esters

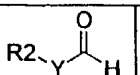
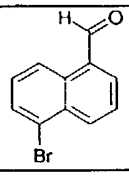
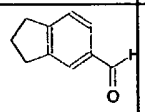
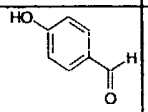
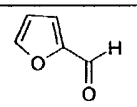
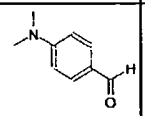
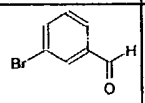
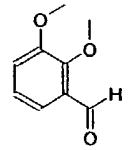
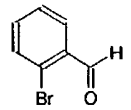
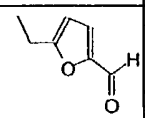
(Method B)

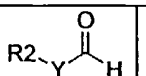
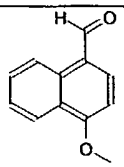
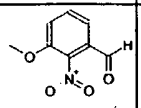
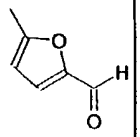
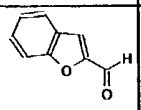
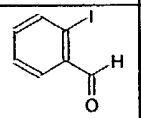
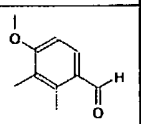
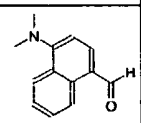
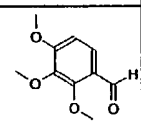
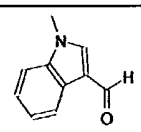


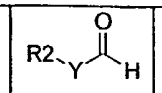
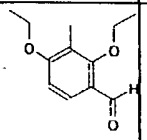
Wang resin with attached 3-carboxy-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (0.88 mmol/g), prepared similarly as described in example was used for this library of compounds. Equal portions of the resin (62 mg, 0.055 mmol) were placed in Teflon tubes equipped with a frit on a mechanical shaker. The resin was allowed to swell in 2 ml dry tetrahydrofuran for 0.5 h, the solvent was removed with suction and the respective aldehyde (0.275 mmol), dissolved in 1 ml tetrahydrofuran was added, followed by 50% v/v acetic acid (0.225 ml). The mixture was shaken under nitrogen atmosphere at room temperature for 0.5 h. A solution of sodium cyanoborohydride (1 M in tetrahydrofuran, 0.20 ml) was added and the mixture was shaken at room temperature for 16 h. The resin was drained, washed with tetrahydrofuran (2x 1 ml), water (2x 1 ml), tetrahydrofuran (2x 1 ml), dichloromethane (2x 1 ml) and tetrahydrofuran/methanol 4:1 (2x 1 ml).

A solution of sodium methoxide (0.009 mmol) in a mixture of tetrahydrofuran/methanol 4:1 (2 ml) was added to the resin and the suspension was agitated at 50 °C for 16 h. The mixture was neutralized by addition of a solution of acetic acid (0.01 mmol) in a mixture of tetrahydrofuran/methanol 4:1 (1 ml), the solution was drained and the resin was washed with tetrahydrofuran (1 ml). The combined filtrates were concentrated in vacuo to yield the title compounds.

Entry	Name		Mw calculated	LC/MS MH+	LC/MS rt[min] (method)
2a	(8-naphthalen-2-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester		443.6	444.2	9.93 (1)
2b	[4-oxo-1-phenyl-8-(3-phenyl-allyl)-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		419.5	420.2	9.8 (1)
2c	[8-(4-nitro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		438.5	439.2	9.43 (1)
2d	(8-benzofuran-7-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester		433.5	434.4	9.00 (1)
2e	[8-(2,2-diphenyl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		483.6	484.4	8.88 (1)
2f	[8-(2-methoxy-naphthalen-1-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		473.6	474.2	9.88 (1)
2g	[8-(4-methoxy-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		423.5	424.2	8.88 (1)
2h	[4-oxo-1-phenyl-8-(2-phenyl-propyl)-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester		421.5	422.4	9.57 (1)

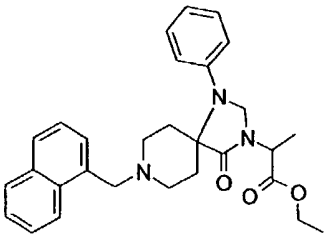
Entry	Name		Mw calculated	LC/MS MH+	rt[min] (method)
2i	[8-(5-Bromonaphthalen-1-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]-acetic acid methyl ester		522.4	522.0	10.77 (1)
2j	(8-Indan-5-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)acetic acid methyl ester		433.6	434.4	10.08 (1)
2k	[8-(4- Hydroxybenzyl)-4-oxo-1-phenyl-1,3,8,triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		409.5	410.4	8.22 (1)
2l	(8-Furan-2-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)acetic acid methyl ester		383.5	384.2	8.30 (1)
2m	[8-(4-Dimethylaminobenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		436.6	437.4	7.85 (1)
2n	[8-(3-Bromobenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		472.4	472.2	9.92 (1)
2o	[8-(2,3-Dimethoxybenzyl)-4-oxo-1-phenyl-1,3,8,triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		453.5	454.4	9.37 (1)
2p	[8-(2-Bromobenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		472.4	474.2	9.37 (1)
2q	[8-(5-Ethylfuran-2-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		411.5	412.2	9.50 (1)

Entry	Name		Mw calculated	LC/MS MH+	rt[min] (method)
2r	[8-(4-Methoxynaphthalen-1-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		473.6	474.2	10.22 (1)
2s	[8-(3-Methoxy-2-nitrobenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		468.5	469.0	9.47 (1)
2t	[8-(5-Methylfuran-2-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		397.5	398.4	9.05 (1)
2u	(8-Benzofuran-2-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)acetic acid methyl ester		433.5	434.4	9.63 (1)
2v	[8-(2-Iodobenzyl)-4-oxo-1-phenyl-1,3,8-triazaapiro[4,5]dec-3-yl]acetic acid methyl ester		519.4	520.2	9.65 (1)
2w	[8-(4-Methoxy-2,3-dimethylbenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3yl]acetic acid methyl ester		451.6	452.4	9.50 (1)
2x	[8-(4-Dimethylaminonaphthalen-1-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		486.6	487.4	8.62 (1)
2y	[8-(2,3,4-trimethoxybenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		483.6	484.4	9.20 (1)
2z	[8-(1-Methyl-1H-indol-3-ylmethyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		446.6	447.2	9.28 (1)

Entry	Name		Mw calculated	LC/MS MH+	rt[min] (method)
2aa	[8-(2,4-Diethoxy-3-methylbenzyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]acetic acid methyl ester		495.6	496.2	11.00 (1)

EXAMPLE 3

2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-propionic acid ethyl ester hydrochloride



, HCl

Sodium hydride, 60% (0.156 g, 3.9 mmol) was suspended in dry heptane (5 ml) and stirred under nitrogen for 5 minutes. The solvent was decanted and dry dimethyl formamide (2 ml) was added. 8-Naphthalen-1-ylmethyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (1.115 g, 3.0 mmol), dissolved in dry dimethyl formamide (11 ml) was added dropwise under cooling in an ice bath. The mixture was stirred at 0 °C for 1 h. An aliquot of the resulting solution of deprotonated 1-phenyl-8-naphthalen-1-ylmethyl-1,3,8-triazaspiro[4.5]decan-4-one (2.3 ml, 0.5 mmol) was added to ethyl 2-bromopropionate and the mixture was stirred at room temperature overnight. Water (15 ml) and ethyl acetate (15 ml) were added and the mixture was shaken, the organic phase was separated and successively washed with water (2 x 10 ml) and brine (10 ml). The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel using a mixture of

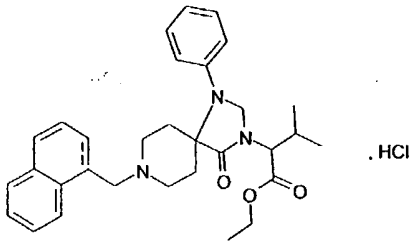
ethyl acetate and dichloromethane 1:4 to give the pure base, which was dissolved in tetrahydrofuran (3 ml) and an excess of a solution of hydrogen chloride in ether was added. Crystallization occured on the careful addition of ether (6 ml). The precipitate was collected by filtration and dried to give the title compound (217 mg, 85% yield).

M.p. 175 - 181 °C.

Calculated for $C_{29}H_{33}N_3O_3$, HCl:
C, 68.56%; H, 6.75%; N, 8.27%; Found :
C, 68.36%; H, 7.03%; N, 7.93%.

Following the same preparation method, the following compounds were prepared:

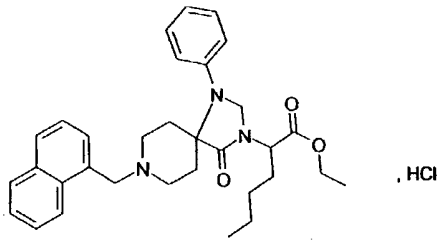
3-Methyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-butyric acid ethylester hydrochloride



LC/MS (Method 2): m/e = 500.2 (MH+); RT = 6.60 min.

Calculated for $C_{31}H_{37}N_3O_3$, HCl, 0.25 H_2O:
C, 69.45%; H, 7.14%; N, 7.84%; Found :
C, 68.87%; H, 7.18%; N, 7.77%.

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-hexanoic acid ethyl ester hydrochloride



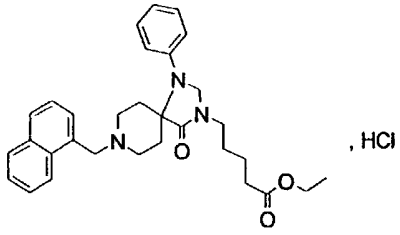
M.p. 169 - 177 °C

Calculated for $C_{32}H_{39}N_3O_3$, HCl, 0.75 H_2O:

C, 68.19%; H, 7.42%; N, 7.45%; Found :

C, 67.92%; H, 7.47%; N, 7.34%.

5-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-pentanoic acid ethyl ester hydrochloride



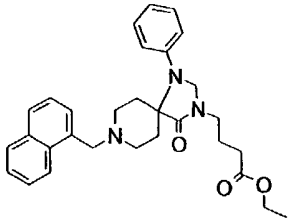
LC/MS (Method 2): m/e = 500.2 (MH+); RT = 6.08 min.

Calculated for $C_{31}H_{37}N_3O_3$, HCl, 1.25 H_2O:

C, 66.12%; H, 7.34%; N, 7.46%; Found :

C, 66.23%; H, 7.13%; N, 7.34%.

4-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-butyric acid ethyl ester hydrochloride



, HCl

M.p. 200 - 203 °C

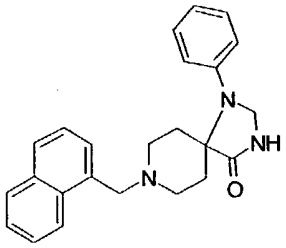
Calculated for $C_{30}H_{35}N_3O_3$, HCl, 0.3 tetrahydrofuran:

C, 68.92%; H, 7.12%; N, 7.73%; Found :

C, 68.63%; H, 7.08%; N, 7.64%.

EXAMPLE 4

8-Naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one



1-Phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (185.04 g, 0.76 mol) was suspended in 2-butanone (3600 ml). 1-(Chloromethyl)naphthalene (169.21 g, 0.91 mol), dry potassium carbonate (345.42 g, 2.50 mol) and sodium iodide (113.91 g, 0.76 mol) were added and the mixture was heated at reflux temperature for 24 h. The solvent was evaporated in vacuo and the remainder was distributed between water (2000 ml) and diethyl ether (2000 ml). The formed precipitate was collected by filtration, washed successively with water (800 ml), toluene (600 ml) and

icecold acetone (2 X 200 ml) and dried affording the title compound as a powder (191.20 g, 68% yield).

M.p. 207 -215 °C

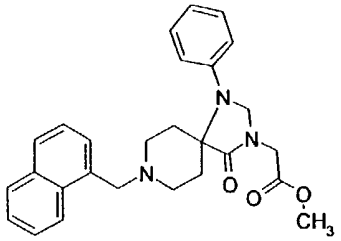
Calculated for $C_{24}H_{25}N_3O$:

C, 77.60%; H, 6.78%; N, 11.31%; Found :

C, 77.23%; H, 6.90%; N, 11.29%.

EXAMPLE 5

(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester



Sodium hydride (60%, 12.96 g, 0.324 mol) was stirred with dry n-heptane under nitrogen and the solvent was decanted from the settled hydride. Icecold dimethyl formamide (600 ml) was added and the resulting solution was added during 0.5 h to a stirred solution of 8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (prepared as described in example 4) in dimethyl formamide (900 ml) at 0 - 5 °C. After stirring for additional 0.5 h, a solution of methyl bromoacetate (54.84 g, 0.348 mol) in dimethylformamide (20 ml) was added under ice cooling. The reaction mixture was allowed to warm up to room temperature while stirring for additional 1 h and was then poured into a mixture of ethyl acetate (800 ml) and ice water (1900 ml) under vigorous stirring. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 X 400 ml). The combined organic phases were successively washed

with water (2 X 300 ml) and brine (2 X 250 ml) and dried over magnesium sulfate. The solution was concentrated in vacuo, ethyl acetate (30 ml) was added to the warm residue under stirring and crystallisation was completed by cooling to room temperature. The product was filtered, washed on the filter with icecold ethyl acetate and dried, to afford the title compound (111.06 g, 83% yield) as a powder.

M.p. 122 - 135 °C

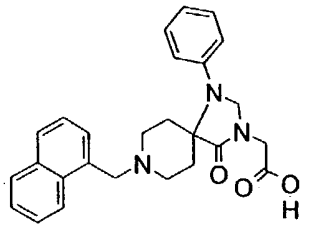
Calculated for $C_{27}H_{29}N_3O_3$:

C, 73.11%; H, 6.59%; N, 9.47%; Found :

C, 72.84%; H, 6.71%; N, 9.36%.

EXAMPLE 6

(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid



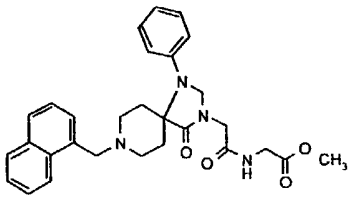
(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester (44.40 g, 0.1 mol, prepared as described above) was dissolved in a mixture of 2 N sodium hydroxide (165 ml, 0.33 mol) and ethanol (500 ml) and stirred at room temperature for 16 h. Dichloromethane (700 ml) was added and pH was adjusted to 5 by the addition of 6 N hydrochloric acid. The organic phase was separated, washed with water (2 x 200 ml and concentrated to 300 ml in vacuo. Water (300 ml) and dichloromethane (100 ml) were added and the slurry was stirred overnight. The product was collected by filtration, washed successively with water (4 x 100 ml, dichloromethane (2 x 50 ml) and acetone (2 x 50 ml) and dried, affording the title compound as a powder (44.6 g, 97% yield).

^{1}H NMR (200 MHz, DMSO-d_6) δ 1.62 (d, 2H), 2.56 (q, 2H), 2.88 (m, 4H), 4.03 (s, 2H), 4.07 (s, 2H), 4.68 (s, 2H), 6.78 (t, 1 H), 6.84 (d, 2H), 7.23 (d, 2H), 7.40 - 7.70 (m, 4H), 7.90 (dd, 2H), 8.42 (d, 1H).

Calculated for $C_{26}H_{27}N_3O_3$, 1.25 H_2O:
C, 69.08%; H, 6.58%; N, 9.30%; Found :
C, 68.89%; H, 6.39%; N, 9.13%.

EXAMPLE 7

(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)acetylglycine methyl ester



Wang resin loaded with Fmoc-glycine (88 mg, 0.045 mmol) was placed in a Teflon tube equipped with a frit on a mechanical shaker. The resin was allowed to swell in dimethyl formamide (1.5 ml) for 1 h. The solvent was removed by suction and the resin was agitated with 20% piperidine in N,N-dimethylformamide (1.5 ml) for 30 minutes. The solution was removed by suction and the resin was washed with N,N-dimethylformamide (3x 1.5 ml). To a solution of (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.0773 g, 0.18 mmol) in dimethyl formamide (1.6 ml), diisopropylcarbodiimide (29 µl, 0.18 mmol) and 1-hydroxy-1H-benzotriazol (0.0243 g, 0.18 mmol) were added and the mixture was stirred at room temperature for 0.5 h. The resulting solution and diisopropylethylamine (31 µl, 0.18 mmol) were added to the above resin and this was shaken at room temperature overnight. The resin was filtered and washed

with dimethylformamide (2 x 1.5 ml), dichloromethane (4 x 1.5 ml), methanol (2 x 1.5 ml) and tetrahydrofuran/methanol 4:1 (2 x 1.5 ml). A solution of sodium methoxide (0.009 mmol) in a mixture of tetrahydrofuran/methanol 4:1 (2 ml) was added to the resin and the suspension was agitated at 50 °C for 16 h. The mixture was neutralized by addition of a solution of acetic acid (0.01 mmol) in a mixture of tetrahydrofuran/methanol 4:1 (1 ml), the solution was drained and the resin was washed with tetrahydrofuran (1 ml). The combined filtrates were concentrated in vacuo to afford the title compound.

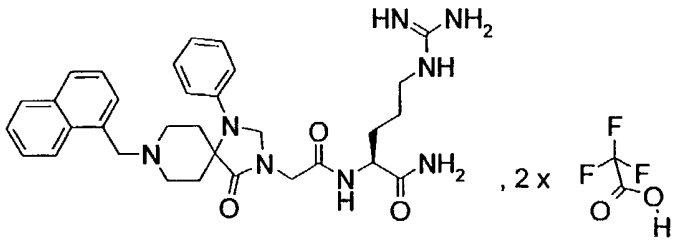
The following compounds were parallel synthesized using the above described method:

Entry	Name	Amino acid-resin	Mw calculated	LC/MS MH+	LC/MS rt[min] (method)
7a	[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetic acid methyl ester	Fmoc-Gly-Wang	500.6	501.4	9.58 (1)
7b	2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionic acid methyl ester	Fmoc-Ala-Wang	514.2	515.4	9.80 (1)
7c	3-Methyl-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid methyl ester	Fmoc-Ile-Wang	556.7	557.4	11.33 (1)
7d	4-Methyl-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-	Fmoc-Leu-	556.7	557.4	11.58 (1)

	spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid methyl ester	Wang			
Entry	**Name**	**Amino acid-resin**	**Mw calculated**	**LC/MS MH+**	**rt[min] (method)**
7e	4-Methylsulfanyl-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-butyric acid methyl ester	Fmoc-Met-Wang	574.7	575.2	10.53 (1)
7f	2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-3-phenyl-propionic acid methyl ester	- Fmoc-Phe Wang	590.7	591.4	11.57 (1)
7g	3-(1H-Indol-3-yl)-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionic acid methyl ester	Fmoc-Trp(Boc)-Wang	629.8	630.4	10.43 (1)
7h	3-Methyl-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-butyric acid methyl ester	Fmoc-Val-Wang	542.7	543.2	10.57 (1)
7i	5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro-[4.5]dec-3-yl)-acetylamino]-pentanoic acid methylester	Fmoc-Arg(Pbf)-Wang	599.7	600.2	8.23 (1)

EXAMPLE 8

5-Guanidino-(S)-2-[2-(8-naphthalen-1-ylmethyl-7-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide, ditrifluoroacetate



One equivalent (1.0 g, 0.69 mmol) of Rink Amide (AM) resin (0.69 mmol/g, purchased from Novabiochem) was suspended in piperidine/N,N-dimethylformamide (20%) (all volumes are calculated as 10 ml/gram of resin) and shaken on a mechanical shaking apparatus for 0.5 h. The resin was filtered, rinsed with N,N-dimethylformamide, suspended in piperidine/N,N-dimethylformamide (20%) and shaken for 0.5 h. The resin was filtered and washed as follows: 3 x N,N-dimethylformamide /water (90%), 2 x ethanol, 3 x N,N-dimethylformamide, 5 x methylene chloride. The resin was dried in vacuo and suspended in N,N-dimethylformamide. Fmoc-Arg(Pbf).OH (1.7 g, 01.7 mmol, 4 equivalents), EDAC (N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride) (0.51 g, 2.68 mmol, 4 equivalents), and HOBT (1-hydroxybenzotriazole) (0.36 g, 2.68 mmol, 4 equivalents) were added and the reaction was allowed to shake for 16 h. The resin was filtered and washed successively with 3 x N,N-dimethylformamide /water (90%), 3 x N,N-dimethylformamide, 3 x methylene chloride, was suspended in piperidine/N,N-dimethylformamide (20%) and shaken for 0.5 h. The resin was filtered and washed as follows: 3 x N,N-dimethylformamide /water (90%), 2 x ethanol, 3 x N,N-dimethylformamide, 5 x methylene chloride. The resin was dried in vacuo and suspended in N,N-dimethylformamide and (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (1.08 g, 2.51 mmol, 3.6 equivalents) was added followed by EDAC (0.47 g, 2.51 mmol, 3.6 equivalents), HOBT (0.33 g, 2.51 mmol, 3.6 equivalents) and the reaction was allowed to stir at room temperature for 20 h. The resin was filtered and washed 3 x N,N-dimethylformamide /water (90%), 3 x N,N-dimethylformamide, 3

x methylene chloride and dried in vacuo. The resin was suspended in trifluoroacetic acid/water (95%) and shaken for 2 h. The filtrate was collected and added dropwise to cyclohexane/ether (50%) after which a white precipitate was observed. This white solid was collected and washed 3 x cyclohexane/ether (50%) with the aid of a centrifuge. This was dissolved in a minimum amount of acetonitrile/water (10%) and lyophilized affording the title compound (273 mg, 50% yield), as a white powder.

HPLC retention time = 11.01 minutes (5 µm C18 4 x 250 mm column, eluting with a 20-80 % gradient of 0.1 % trifluoroacetic acid/acetonitrile and 0.1 % trifluoroacetic acid/water over 30 minutes at 35 °C).

LC/MS (Method 2): m/e = 585.4 ((MH+); RT = 4.43 min.

5-Guanidino-(R)-2-[2-(8-naphthalen-1-ylmethyl-7-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide, di-trifluoroacetate

This compound was prepared and purified analogously to EXAMPLE 8 using Rink Amide (AM) Resin (0.69 mmol/g) (0.200 g, 0.138 mmol, 1 equivalent), Fmoc-.D-Arg(Pbf).OH (0.358 g, 0.552 mmol, 4 equivalents) to yield the title compound (73 mg, 59% yield) as a white powder. This powder was assumed to be salted with two equivalents of trifluoroacetic acid.

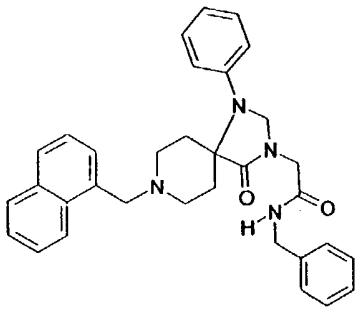
LC/MS (Method 2): m/e = 585.2 (MH^+); RT = 4.42 min.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.4 (bm, 3H), 1.7 (bm, 1H), 1.8-1.9 (bm, 2H), 2.8 (bm, 2H), 3.1 (m, 2H), 3.4-3.5 (bm, 4H), 3.7 (bm, 1H), 4.1 (s, 2H), 4.2 (m, 1H), 4.6 (m, 2H), 4.8-4.9 (bm, 1H), 6.6-7.4 (bm, 4H), 6.7 (m, 1H), 6.9 (m, 2H), 7.1 (s, 1H), 7.2 (t, J= 9 Hz, 2H), 7.4 (s, 1H), 7.0-7.2 (m, 4H), 7.9 (bs, 1H), 8.0 (m, 2H), 8.4 (t, J= 9 Hz, 2H), 10.2 (bs, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 24.62, 25.94, 28.61, 42.37, 48.19, 51.63, 57.22, 63.14, 114.17, 118.02, 123.53, 124.84, 125.77, 126.57, 128.31, 128.70, 131.64, 132.97, 141.91, 156.23, 166.06, 172.62, 6 carbons obscured.

EXAMPLE 9A

N-Benzyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide



To a suspension of the the commercially available aminomethylated polystyrene resin (Novabiochem) (20 g, 16 mmol) in dimethylformamide (70 ml) was added a solution of the commercially available BAL-Linker (PerSeptive Biosystems GMBH) (12.88 g, 48.0 mmol) and 1-hydroxybenzotriazole (7.26 g, 48.0 mmol) in 70 ml of dimethylformamide. To this was added N,N'-diisopropylcarbodiimide (6.06 g, 48.0 mmol) followed by N,N-diisopropylethylamine (6.19 g, 48.0 mmol). The reaction was allowed to stir 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide (50 ml), 3 x tetrahydrofuran (50 ml), 3 x dichloromethane (50 ml), 3 x ether (50 ml). The resin was dried in vacuo and isolated: 23.92 g. IR spectroscopy showed an aldehyde stretching band at 1674 cm^{-1}. To a part of this resin (0.200 g, 0.160 mmol) in 1,2-dichloroethane (8 ml) at room temperature, was added benzyl amine (0.171 g, 1.60 mmol) followed by sodium triacetoxyborohydride (0.339 g, 1.60 mmol). The reaction was allowed to shake 20 h at room temperature, filtered and washed as follows: 3 x dimethylformamide /water (90/10) (8 ml); 3 x dimethylformamide (8 ml); 3 x di-

chloromethane (8 ml). The resin was suspended in dimethylformamide, treated with (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.274 g, 0.640 mmol), 1-hydroxybenzotriazole (0.099 g, 0.640 mmol) and N,N'-diisopropylcarbodiimide (0.081 g, 0.640 mmol). The reaction was allowed to shake for 20 h at room temperature. The resin was filtered, suspended in dimethylsulfoxide and heated to 40 °C for 1 h. The resin was again filtered, suspended in dimethylsulfoxide (8 ml) and heated to 40 °C for 1 h. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml); 3 x dimethylformamide (8 ml); 3 x dichloromethane (8 ml) and air-dried. The resin was treated with trifluoroacetic acid/water (95/5) (8 ml) for 1 h at room temperature. The filtrate was collected and concentrated in vacuo to give the desired product.

The above example and the following compounds were synthesized in a parallel fashion using the above procedure and the appropriate amine.

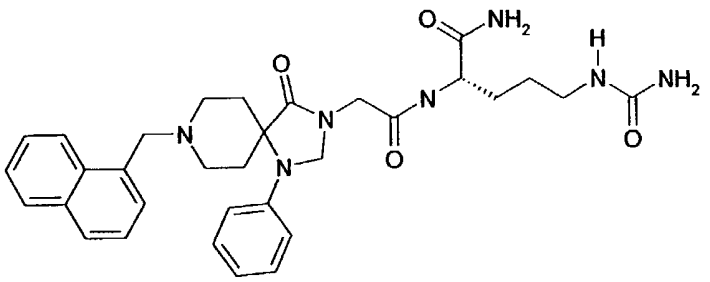
Entry	Name	Amine	MW calculated	LCMS MH+	rt(min) (method)
9a	N-benzyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	benzylamine	518	519	5.34 (2)
9b	N-phenethyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	phenethylamine	532	533	5.40 (2)
9c	N-(N-3-propylmorphoino)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	N-(3-aminopropyl)-morpholine	555	556	4.27 (2)
9d	N-hexyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-	N-hexylamine	512	513	5.90 (2)

	spiro[4.5]dec-3-yl)-acetamide				
9e	N-furfuryl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	furfurylamine	508	509	5.10 (2)
9f	N-(3-phenyl-1-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	3-phenyl-1-propyl-amine	546	547	5.60 (2)
9g	N-(2-methoxyethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	2-methoxyethyl-amine	486	487	4.67 (2)
9h	N-(cyclohexanemethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	cycohexane-methylamine	524	525	6.04 (2)
9i	N-(4-methoxybenzyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	4-methoxybenzyl-amine	548	549	5.34 (2)
9j	N-pipieronyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	piperonylamine	562	563	5.30 (2)
9k	N-(tetrahydrofurfuryl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	tetrahydrofurfuryl-amine	512	513	4.74 (2)
9l	N-(2-methoxyphenyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-	2-methoxyphen-ethylamine	562	563	5.64 (2)

	spiro[4.5]dec-3-yl)-acetamide				
9m	N-(4-phenylbutyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	4-phenylbutyl-amine	560	561	6.17 (2)
9n	N-[4-(2-aminoethyl-pyridine)]-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	4-(2-aminoethyl)-pyridine	533	534	4.40 (2)
9o	N-(4-methoxyphenethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	4-methoxyphen-ethylamine	562	563	5.30 (2)
9p	N-[1-(3-aminopropyl)-2-pyrrolidnonyl]-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	1-(3-aminopropyl)-2-pyrrolidinone	553	554	4.70 (2)
9q	N-napthylenemethyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	1-napthalene-methylamine	568	569	6.17 (2)
9r	N-[4-(tert-butyl)benzyl]-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	4-(tert-butyl)benzylamine	574	575	6.51 (2)
9s	N-(2-phenoxyethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)-acetamide	2-phenoxy-ethylamine	548	549	5.37 (2)

EXAMPLE 10A

2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-5-ureido-pentanoic acid amide



Rink Amide (AM) resin (Novabiochem) (0.200 g, 0.138 mmol) was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide (8 ml) and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml), Fmoc-L-2-amino-5-ureido-n-valeric acid (L-Fmoc-Cit-OH) (0.227 g, 0.552 mmol) and 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) were added. N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) was added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide (8 ml) and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml); (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.269 g,

0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added. The reaction mixture was allowed to shake at room temperature for 20 h and filtered. The resin was suspended in dimethylsulfoxide (8 ml) and heated to 40 °C for 1 h. The resin was again filtered, suspended in dimethylsulfoxide (8 ml) and heated to 40 °C for an additional 1 h. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml); 3 x dimethylformamide (8 ml); 3 x dichloromethane (8 ml) and air-dried. The resin was treated with trifluroacetic acid/water (95/5) (8 ml) for 2 h at room temperature. The filtrate was collected and concentrated in vacuo to give the desired product.

The above example and the following examples were synthesized in a parallel manner using the procedure outlined above with the appropriate L-Fmoc-protected amino acid. For examples 10b and 10c, the TFA/water cleavage filtrate was added dropwise into a solution of heptane/ether (50/50) (10 ml) at 0 °C. Compound 10b precipitated and was collected as a white solid. For example 10c, an oily residue was formed, the heptane/ether solution was decanted, the residue was taken up into water/acetonitrile (90/10) (10 ml) and freeze-dried to give a white powder.

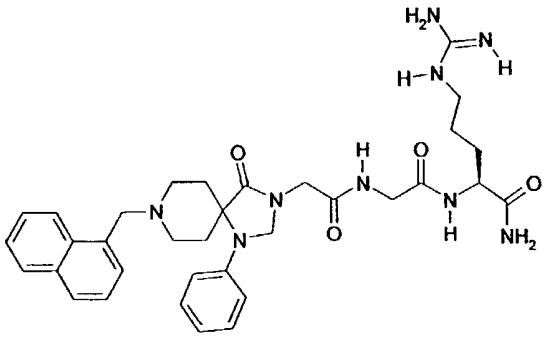
Entry	Name	L-Amino Acid	MW calculated	LCMS MH+ rt(min) (method)	
10a	2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-5-ureido-pentanoic acid amide	Fmoc-Cit-OH	472	586	4.40 (2)
10b	2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanedioic acid diamide	Fmoc-Gln(trt)-OH	556	557	4.47 (2)
10c	3-[(1H-Imidazol-4-yl)-2-	Fmo-His(trt)-OH	565	566	4.14

	(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide				(2)
10d	6- [Amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoic acid amide	Fmoc-Lys(Boc)-OH	556	557	4.27 (2)
10e	1-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetyl]-pyrrolidine-2-(S)-carboxylic acid amide	Fmoc-Pro-OH	525	526	4.64 (2)
10f	3-Hydroxy-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide	Fmoc-Ser(t-Bu)-OH	515	516	4.50 (2)
10h	3-(1H-Indol-3-yl)-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide	Fmoc-Trp(Boc)-OH	614	615	5.04 (2)
10h	3-(4-Hydroxy-phenyl)-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide	Fmoc-Tyr(t-Bu)-OH	591	592	4.77 (2)
10i	N-Carbamoylmethyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide	Fmoc-Gly-OH	485	486	4.44 (2)
10j	2-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-2-(S)-phenyl-acetamide	Fmoc-Phg-OH	561	562	5.47 (2)

EXAMPLE 11A

5-Guanidino-2-(S)-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-pentanoic acid amide

5



Rink Amide (AM) resin (Novabiochem) (0.200 g, 0.138 mmol) was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide(8 ml), 3 x dichloromethane. The resin was suspended in dimethylformamide (8 mL), L-Fmoc-Arg(Pbf)-OH (0.358 g, 0.552 mmol) and 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) were added. N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) was added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml), Fmoc.Gly.OH (0.163 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added. The reaction was allowed to shake 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (80/20) (8 ml), 3 x dimethylformamide (8

ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml); (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.269 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added. The reaction mixture was allowed to shake at room temperature for 20 h and filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml); 3 x dimethylformamide (8 ml); 3 x dichloromethane (8 ml) and air-dried. The resin was treated with trifluoroacetic acid/water (95/5) (8 ml) for 2 h at room temperature. The filtrate was collected and added dropwise to cyclohexane/ether at 0 °C to form a white precipitate.

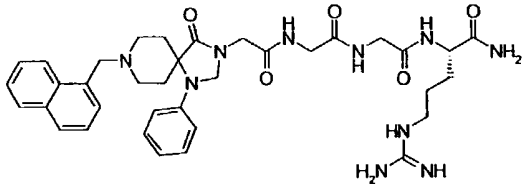
The above and following examples were prepared according to this procedure using the appropriate amino acids as outlined in the table below.

Entry	Name	L-Amino Acids	MW calculated	LCMS MH+ rt(min) (method)	
11a	5-Guanidino-2-(S)-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-pentanoic acid amide	Fmoc-Arg(Pbf)-OH Fmoc-Gly-OH	641	642	4.07 (2)
11b	5-Guanidino-2-(S)-(2-{methyl-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetyl]-amino}-acetylamino)-pentanoic acid amide	Fmoc-Arg(Pbf)-OH Fmoc-Sar-OH	655	656	4.30 (2)

11c	5-Guanidino-2-(S)-{3-naphthalen-2-yl-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionylamino}-pentanoic acid amide	Fmoc-Arg(Pbf)-OH Fmoc-β-(2-naphthyl)-Ala-OH	781	782	4.54 (2)

EXAMPLE 12

5-Guanidino-2-(S)-(2-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-acetylamino)-pentanoic acid amide



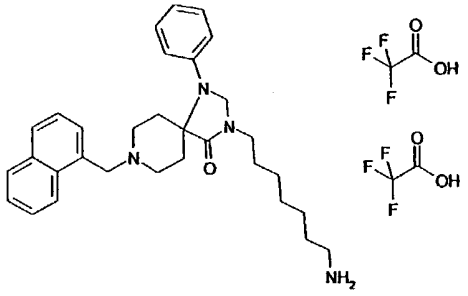
Rink Amide (AM) resin (Novabiochem) (0.200 g, 0.138 mmol) was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml), **L**- Fmoc-Arg(Pbf)-OH (0.358 g, 0.552 mmol) and 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) were added. N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) was added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethyGformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for

30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml), Fmoc-Gly-Gly-OH (0.195 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml); (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.269 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added. The reaction mixture was allowed to shake at room temperature for 20 h, filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml); 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was treated with trifluoroacetic acid/water (95/5) (8 ml) for 2 h at room temperature. The filtrate was collected and added dropwise to cyclohexane/diethylether (50/50) at 0 °C to form a white precipitate which was collected and washed with the cyclohexane/diethylether solution. 32.5 mg of product were collected.

Calculated MW= 698, LCMS (method 2), retention time= 4.20 min, MH+= 699.

EXAMPLE 13

3-(7-Aminoheptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, ditrifluoroacetate



Sodium hydride, 60% (0.156 g, 3.9 mmol) was suspended in dry heptane (5 ml) and stirred under nitrogen for 5 minutes. The solvent was decanted and dry dimethyl formamide (4 ml) was added. 8-Naphthalen-1-ylmethyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (1.115 g, 3.0 mmol), dissolved in dry dimethyl formamide (11 ml) was added dropwise under cooling in an ice bath. The mixture was stirred at 0 °C for 1 h. The resulting solution of deprotonated 1-phenyl-8-naphthalen-1-ylmethyl-1,3,8-triazaspiro[4.5]decan-4-one was added dropwise to a stirred solution of 1,7-dibromoheptane (3.88 g, 15 mmol) in dimethyl formamide (3 ml) at room temperature and stirring was continued for 1 h. The mixture was then diluted with water (50 ml) and extracted with ethyl acetate (2x 30 ml). The combined organic phases were successively washed with water (2 X 20 ml) and brine (2x 20 ml), dried over $MgSO_4$ and evaporated in vacuo. The residue was dissolved in a mixture of tetrahydrofuran (10 ml) and ether (10 ml) and the hydrochloride was precipitated by the dropwise addition of a solution of hydrogen chloride in ether in excess. The precipitate was washed with a 1:1 mixture of tetrahydrofuran and ether and dried, affording 3-(7-bromo-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (1.192 g, 68% yield) as a powder.

LC/MS (Method2): m/e = 550.2 (MH^+); RT = 6.74 min.

1H NMR (200 MHz, $CDCl_3$) d 1.4 (bm, 6H), 1.5-1.9 (m, 6H), 3.3-3.6 (m, 8H), 3.92 (broad dd, 2H), 4.70 (s, 4H), 6.86 (t, 1H), 7.15 (d, 2H), 7.35 (t, 2H), 7.5-7.7 (m, 3H), 7.92 (dd, 2H), 8.15 (d, 1H), 8.38 (d, 1H).

The above bromide (0.38 g, 0.65 mmol) was dissolved in a 5 M ammonia solution in ethanol (7.5 ml) and heated in an autoclave at 100 °C for 16 h. The solution was evaporated in vacuo and the residue was purified by preparative HPLC using a C18-silica column. The column was eluted with a linear gradient of 10-90% acetonitril and 90-10% 0.1% trifluoroacetic acid in 15 minutes. The pure fraction was evaporated in vacuo, dissolved in water/acetonitrile and freeze dried, to afford the title compound (0.238 g, 51% yield) as a powder.

LC/MS (Method2): m/e = 485.4 (MH^+); RT = 4.77 min

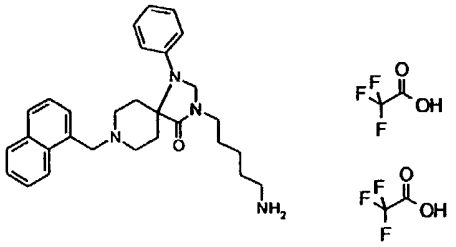
Calculated for $C_{31}H_{40}N_4O$, 2 CF_3CO_2H, 0.5 H_2O:

C, 58.25%; H, 6.00%; N, 7.76%; Found :

C, 58.20%; H, 6.13%; N, 7.23%.

The following compounds were synthesized using the above procedure and the appropriate dihaloalkane:

3-(5-Aminopentyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, di-trifluoroacetate



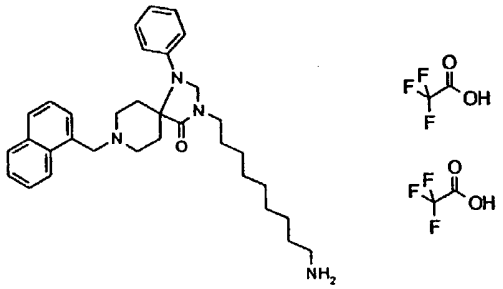
LC/MS (Method2): m/e = 457.4 (MH^+); RT = 5.17 min

Calculated for $C_{29}H_{36}N_4O$, 2 CF_3CO_2H:

C, 57.89%; H, 5.59%; N, 8.18%; Found :

C, 57.57%; H, 5.54%; N, 8.05%.

3-(9-Aminononyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one di-trifluoroacetate



LC/MS (Method2): m/e = 513.6 (MH^+); RT = 5.03 min

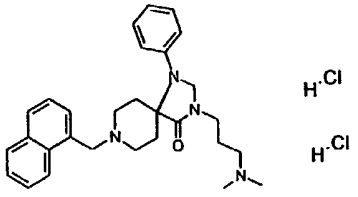
Calculated for $C_{33}H_{44}N_4O$, 2.4 CF_3CO_2H:

C, 57.73%; H, 5.95%; N, 7.12%; Found :

C, 57.75%; H, 6.07%; N, 7.17%.

EXAMPLE 14

3-(3-Dimethylaminopropyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one dihydrochloride



3-(3-chloropropyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.145 g, 0.30 mmol), prepared using the procedure described in Example 13, was added to a 33% solution of dimethylamine in ethanol. Sodium iodide (0.045 g, 0.3 mmol) was added and the mixture was stirred at room temperature

for 24 h. Salts were separated by filtration and the filtrate was evaporated in vacuo. The residue was purified by flash chromatography on silica gel using dichloromethane/ ethyl acetate 1:1 containing 2.5% triethylamine as the eluent. The pooled pure fractions were evaporated in vacuo and the residue dissolved in tetrahydrofuran (5 ml) and the hydrochloride was precipitated by the dropwise addition of a solution of hydrogen chloride in ether in excess. The precipitate was collected by filtration and dried, affording the title compound (148 mg, 93% yield) as a powder.

LC/MS (Method2): m/e = 457.4 (MH^+); RT = 4.47 min

Calculated for $C_{29}H_{36}N_4O$, 2 HCl, 2 H_2O:

C, 61.59%; H, 7.48%; N, 9.60%; Found :

C, 61.56%; H, 7.23%; N, 9.30%.

The following compound was synthesized using the above procedure.

3-(7-Dimethylaminoheptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one dihydrochloride

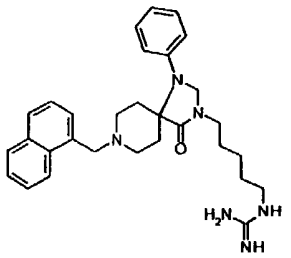
The compound was synthesized using 3-(7-bromo-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, prepared as described in Example 13.

LC/MS (Method2): m/e = 513.6 (MH^+); RT = 4.77 min

^1H NMR (400 MHz, $CDCl_3$) d 1.4 (m, 6H), 1.65 (m, 2H), 1.74 (d, 2H), 1.87 (m, 2H), 2.80 (s, 6H), 3.35-3.55 (m, 6H), 3.90 (m, 2H), 4.72 (s, 4H), 6.85 (t, 1H), 7.13 (d, 2H), 7.35 (t, 2H), 7.55-7.70 (m, 3H), 7.95 (t, 2H), 8.17 (d, 1H), 8.33 (d, 1H), 12.4 (broad s, 1H), 12.7 (broad s, 1H).

EXAMPLE 15

N-(5-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8,-triazaspiro[4.5]dec-3-yl)pentyl)guanidine



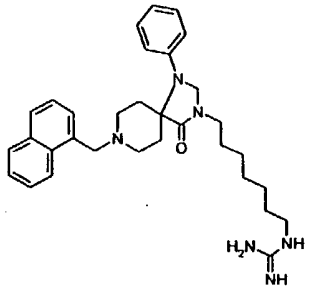
3-(5-Aminopentyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, di-trifluoroacetate (0.137 g, 0.2 mmol) prepared as described in Example 13, was dissolved in dimethylformamide (1 ml) and diisopropylethylamine (0.233 g, 1.8 mmol) and 3,5-dimethylpyrazol-1-carboxamidine nitrate (0.060 g, 0.3 mmol) was added. The mixture was stirred at room temperature for 1 h and the addition of an equal amount 3,5-dimethylpyrazol-1-carboxamidine nitrate was repeated. After stirring for 16 h the mixture was diluted with water (10 ml) and extracted with ether (5x 10 ml). The aqueous phase and undissolved syrup were extracted with dichloromethane (10 ml), the dichloromethane solution was washed with water (5x 10 ml), dried over $MgSO_4$ and concentrated in vacuo, affording the title compound (0.047 g, 5.2%) as an amorphous powder.

LC/MS (Method2): m/e = 499.2 (MH^+); RT = 4.70 min

^1H NMR (400 MHz, DMSO-d_6) d 1.3 (m, 2H), 1.45-1.65 (m, 7H), 2.48 (m, 1H), 2.32 (m, 4H), 3.09 (t, 2H), 3.35 (t, 2H), 3.95 (s, 2H), 4.68 (s, 2H), 6.79 (t, 1H), 6.88 (d, 2H), 7.23 (t, 2H), 7.50 (d, 2H), 7.59 (dt, 2H), 7.88 (dd, 1H), 7.95 (d, 1H), 8.40 (d, 1H).

The following compound was synthesized using the above procedure:

N-(5-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8,-triazaspiro[4.5]dec-3-yl)heptyl)guanidine

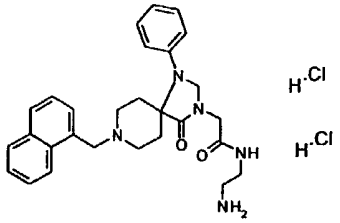


LC/MS (Method2): m/e = 527.2 (MH^+); RT = 4.90 min

^1H NMR (200 MHz, DMSO-d_6) d 1.2-1.4 (m, 6H), 1.45-1.70 (m, 6H), 2.5-2.9 (m, 6H), 3.15 (m, 2H), 3.35 (t, 2H), 3.95 (s, 2H), 4.62 (s, 2H), 6.80 (m, 3H), 7.23 (t, 2H), 7.30-7.7 (m, 5H), 7.75 (m, 2H), 8.40 (d, 1H).

EXAMPLE 16

N-(2-Aminoethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)acetamide dihydrochloride



The p-nitrophenylcarbonate derivative of Wang resin was treated with 1,2-diaminoethane according to the procedure described in Tetrahedron Letters, 1995, 36, p. 8677. The resulting resin (2.87 g, 2.5 mmol) was placed in a solid synthesis flask equipped with a glass frit and swelled in dry dimethylformamide (50 ml) for 30 minutes and the excess solvent was removed by suction.

To a suspension of (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (4.88 g, 10 mmol) in dimethyl formamide (30 ml) in a separate flask was added 1-hydroxybenzotriazol (1.35 g, 10 mmol) and diisopropylcarbodiimide (1.26 g, 10 mmol). The mixture was stirred at room temperature for 1 h and then added to the above resin. Diisopropylamine (1.29 g, 10 mmol) was added and the mixture was agitated on a shaker for 16 h. . The solution was removed by suction and the resin was washed with dimethylformamide (2x 50 ml), dimethylsulfoxide (2x 50 ml), dichloromethane (4x 50 ml), methanol (3x 50 ml) and dichloromethane (1x 50 ml). A 1:1 mixture of dichloromethane/trifluoroacetic acid (25 ml) was added and the resin was agitated for 30 min. The solution was drained and the resin was washed with dichloromethane (2x 25 ml). The combined filtrates were concentrated in vacuo and the residue was shaken with dichloromethane (50 ml) and saturated $NaHCO_3$-solution (25 ml). The organic phase was washed with water (20 ml) and brine (20 ml) and concentrated in vacuo. The residue was dissolved in tetrahydrofuran and a solution of hydrogen chloride in ether was added. The formed precipitate was collected by filtration and dried to afford the title compound (0.67 g, 49%) as a powder.

LC/MS (Method2): m/e = 472.2 (MH^+); RT = 4.27 min

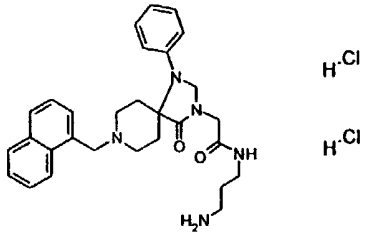
Calculated for $C_{28}H_{33}N_5O_2$, 2 HCl, 3 H_2O:

C, 56.19%; H, 6.90%; N, 11.70%; Found :

C, 56.03%; H, 6.45%; N, 11.34%.

The following compound was synthesized using the above procedure:

N-(3-Aminopropyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)acetamide dihydrochloride



The 1,3-diaminopropyl Wang resin was prepared using the procedure described above.

LC/MS (Method2): m/e = 486.4 (MH^+); RT = 4.27 min

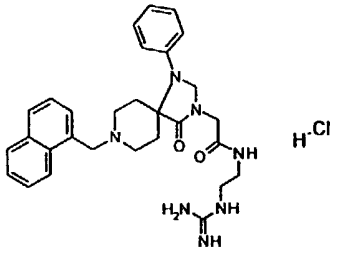
Calculated for $C_{29}H_{35}N_5O_2$, 2 HCl, 2.75 H_2O:

C, 57.28%; H, 7.64%; N, 11.52%; Found :

C, 57.16%; H, 7.72%; N, 11.20%.

EXAMPLE 17

N-(2-Guanidinoethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8,-triazaspiro[4.5]dec-3-yl)acetamide hydrochloride



To a solution of N-(2-aminoethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl)acetamide dihydrochloride (0.203 g, 0.40 mmol) in dimethylformamide (1.5 ml) was added diisopropylethylamine (0.046 g, 3.6 mmol) and 1-H-pyrazole-1-carboxamidine hydrochloride (0.088 g, 0.60 mmol). The mixture was stirred at room temperature for 1 h and the same amount of 1-H-

pyrazole-1-carboxamidine hydrochloride was added. The reaction was stirred for further 48 h, water (10 ml) was added and the solution was washed with ether (5x 10 ml). The aqueous phase was adjusted to pH 1 with diluted hydrochloric acid, washed with dichloromethane (20 ml), adjusted to pH 8 with diluted sodium hydroxide solution and extracted with dichloromethane (3x 5 ml). The organic phase was concentrated to 5 ml and left for crystallization in a refrigerator.

The precipitate was filtered and dried, affording the title compound (135 mg, 66%) as a powder.

LC/MS (Method2): m/e = 514.4 (MH^+); RT = 4.37 min

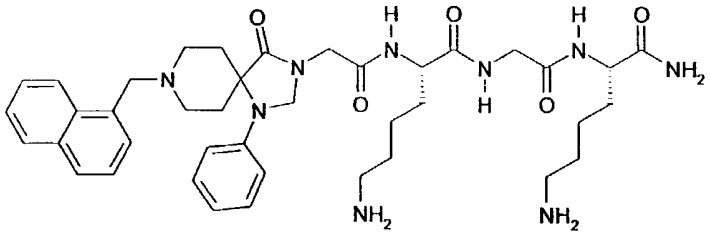
Calculated for $C_{29}H_{35}N_7O_2$, HCl, 0.7 H_2O:

C, 61.90%; H, 6.70%; N, 17.42%; Found :

C, 61.95%; H, 6.52%; N, 17.30%.

EXAMPLE 18

6-Amino-2-(S)-(2-(S)-{6-amino-2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoylamino}-acetylamino)-hexanoic acid amide



Rink Amide (AM) resin (Novabiochem) (0.200 g, 0.138 mmol) was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide (8 ml) and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane

(8 ml). The resin was suspended in dimethylformamide (8 ml), L Fmoc-Lys(Boc)-OH (0.258 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide (8 ml) and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml); Fmoc-Gly-OH (0.163 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide and again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml); L-Fmoc-Lys(Boc)-OH (0.258 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added and the reaction was allowed to shake for 20 h at room temperature. The resin was filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature. The resin was filtered and rinsed with dimethylformamide (8 ml) and

again suspended in dimethylformamide/piperidine (80/20) (8 ml) and shaken for 30 min at room temperature; the resin was washed as follows: 3 x dimethylformamide/water (90/10) (8 ml), 3 x dimethylformamide (8 ml), 3 x dichloromethane (8 ml). The resin was suspended in dimethylformamide (8 ml); (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.269 g, 0.552 mmol), 1-hydroxybenzotriazole (0.085 g, 0.552 mmol) and N,N'-diisopropylcarbodiimide (0.071 g, 0.552 mmol) were added. The reaction mixture was allowed to shake at room temperature for 20 h, filtered and washed as follows: 3 x dimethylformamide/water (90/10) (8 ml); 3 x dimethylformamide; 3 x dichloromethane (8 ml). The resin was treated with trifluoroacetic acid/water (95/5) (8 ml) for 2 h at room temperature. The filtrate was collected and added dropwise to heptane/diethylether at 0 °C to form a white precipitate which was collected and washed with the heptane/diethylether solution. 13.7 mg of product were isolated.

Calculated MW= 741, LCMS (method 2) shows retention time= 3.80 min, MH+= 742.

CLAIMS:

1. Use of a small organic compound acting as an opioid receptor ligand for the preparation of a pharmaceutical composition for the treatment of a disease selected from migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence, vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes and/or for alleviating symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

2. Use of a small organic compound according to claim 1 acting as a Nociceptin receptor ligand with a molecular weight of less than 1000 or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

3. Use of a small organic compound according to any of the claims 1-2 acting as a Nociceptin receptor ligand with a molecular weight less than 600 or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

4. Use of a small organic compound according to any of the claims 1-3 acting as a Nociceptin receptor ligand with less than 5 amide bonds or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

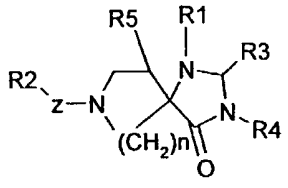
5. Use of a small organic compound according to any of the claims 1-3 acting as a Nociceptin receptor ligand wherein said compound has no amide bonds or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

6.

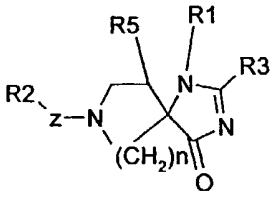
7. Use of a compound according to any of the claims 1-5 wherein said compound comprises a triaza-spiro compound acting as a Nociceptin receptor ligand or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

8. Use of a small organic compound according to any of the claims 1-6 acting as a Nociceptin receptor ligand with an IC_{50} less than 1μM or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

9. A compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$ where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group;

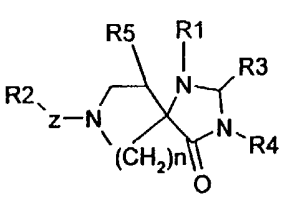
R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

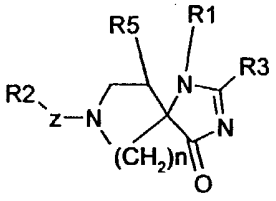
n is 1 or 2

or a pharmaceutically acceptable salt thereof.

9. A compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, -OH, an amino acid residue, $NR^{14}R^{15}$ or C_{1-6}-alkoxy, wherein R^{14} and R^{15} independently are hydrogen or C_{1-6} alkyl and A is $-CH_2$ or -C=O;

provided that when R^{11} is an amino acid residue, then A is a -C=O group;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

n is 1 or 2

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 8-9 wherein R^1 is C_{1-6}-alkyl, phenyl, arylalkyl or thienyl.

11. A compound according to any of the claims 8-10 wherein

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of fluorine, chlorine, bromine, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl

or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of fluorine, chlorine, bromine, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl or a pharmaceutically acceptable salt thereof.

12. A compound according to any of the claims 8-11 wherein

R^4 is hydrogen or $(CH_2)_m(CHR^9)$-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is -OH, $-NR^{14}R^{15}$ or C_{1-6}-alkoxy, wherein R^{14} and R^{15} are hydrogen or C_{1-6} alkyl and A is C=O or a pharmaceutically acceptable salt thereof.

13. A compound according to any of the claims 8-12 selected from the following:

(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,
{8-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester,
[8-(3-Cyano-3,3-diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,
[8-(4-Nitro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,
[4-Oxo-1-phenyl-8-(3-phenyl-propyl)-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,
[4-Oxo-8-(3-phenoxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,
[4-Oxo-8-(4-phenoxy-butyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,
[8-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,
{8-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester,
(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,
{8-[2-(4-Fluoro-phenoxy)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester,

[8-(6,7-Dimethoxy-2-oxo-2H-chromen-4-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(3-Cyano-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

3-(3-Methoxycarbonylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-benzoic acid methyl ester,

[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

(8-Anthracen-9-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester ,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]pentanoic acid methylester,

N-(2-Guanidino-ethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

3-(7-Amino-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

3-(1H-Imidazol-4-yl)-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

5-Guanidino-2-(R)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

N-(3-Guanidino-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

3-(5-Amino-pentyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

N-(3-Amino-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

N-(2-Amino-ethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

N-[7-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-heptyl]-guanidine,

3-Ethyl-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-N-(tetrahydro-furan-2-ylmethyl)acetamide,

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-N-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-acetamide,

6-Amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoic acid amide,

N-Carbamoylmethyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-phenyl-acetamide,

6-Amino-2-(S)-(2-{6-amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoylamino}-acetylamino)-hexanoic acid amide,

5-Guanidino-2-(S)-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-pentanoic acid amide,

5-Guanidino-2-(S)-(2-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-acetylamino)-pentanoic acid amide,

(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,

[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

5-Guanidino-2-(R)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide or

3-(7-Amino-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

14. A pharmaceutical composition comprising as active component a compound according to any of the claims 8-13 together with a pharmaceutical acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition suitable for use in the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances comprising an amount of compound according to any of the claims 8-13 together with a pharmaceutical carrier or diluent.

16. A pharmaceutical composition according to any of the claims 14 or 15 wherein it is in a form of an oral dosage unit or a form suitable for oral, nasal, transdermal, pulmonal parenteral dosage unit containing 0.1 to about 1000 mg per patient per day.

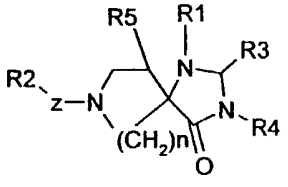
17. Use of a compound according to any of the claims 8-13 for the preparation of a medicament for treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances.

18. Use of a compound according to any of the claims 8-13 for the preparation of a medicament for treatment of vasomotor disturbances, especially hot flushes.

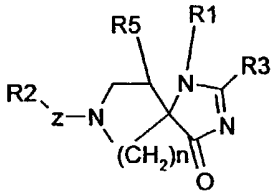
19. A method of treating hot flushes in a subject in need of such treatment comprising the step of administering to said object an amount of a compound according to any of the claims 8-13which is effective for the alleviation of such ailment.

20. A method of treating hot flushes in a subject in need of such treatment comprising the step of administering to said object an amount of a compound according to any of the claims 8-13 which is effective for the alleviation of such ailment in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

21. Use of a compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogene, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is

phenyl, phenoxy, benzodioxinyl, cyanodiphenylmethyl, aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumari-

nyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$ where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

n is 1 or 2

or a pharmaceutically acceptable salt thereof for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence, vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes and/or for alleviating symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

AMENDED CLAIMS

[received by the International Bureau on 18 October 1999 (18.10.99);
Original claims 1-21 replaced by new claims 1-21; (11 pages)]

1. Use of a small organic compound acting as an opioid receptor ligand for the preparation of a pharmaceutical composition for the treatment of a disease selected from migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence, vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes and/or for alleviating symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

2. Use of a small organic compound according to claim 1 acting as a Nociceptin receptor ligand with a molecular weight of less than 1000 or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

3. Use of a small organic compound according to any of the claims 1-2 acting as a Nociceptin receptor ligand with a molecular weight less than 600 or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

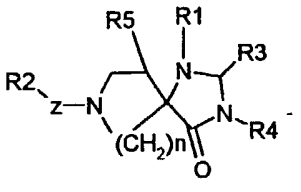
4. Use of a small organic compound according to any of the claims 1-3 acting as a Nociceptin receptor ligand with less than 5 amide bonds or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

5. Use of a small organic compound according to any of the claims 1-3 acting as a Nociceptin receptor ligand wherein said compound has no amide bonds or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

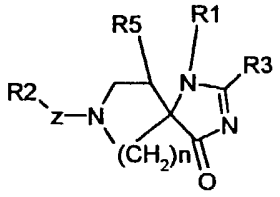
6. Use of a compound according to any of the claims 1-5 wherein said compound comprises a triaza-spiro compound acting as a Nociceptin receptor ligand or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

7. Use of a small organic compound according to any of the claims 1-6 acting as a Nociceptin receptor ligand with an IC_{50} less than 1μM or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of vasomotor disturbances.

8. A compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-

alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$ where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group;

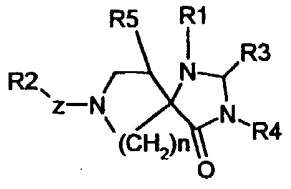
R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

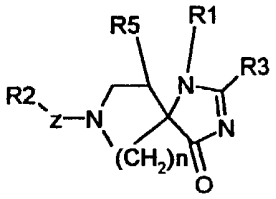
n is 1 or 2

or a pharmaceutically acceptable salt thereof.

9. A compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, -OH, an amino acid residue, $NR^{14}R^{15}$ or C_{1-6}-alkoxy, wherein R^{14} and R^{15} independently are hydrogen or C_{1-6} alkyl and A is $-CH_2$ or -C=O;

provided that when R^{11} is an amino acid residue, then A is a -C=O group;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

n is 1 or 2

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 8-9 wherein R^1 is C_{1-6}-alkyl, phenyl, arylalkyl or thienyl.

11. A compound according to any of the claims 8-10 wherein

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of fluorine, chlorine, bromine, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl

or

R^2 is phenyl, phenoxy, benzodioxinyl or cyanodiphenylmethyl, any of which may be substituted with one or more of fluorine, chlorine, bromine, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl, provided that R^1 is not phenyl, R^3 is not methyl or hydrogen or R^4 is not hydrogen, acetyl, methyl, hydroxymethyl, ethyl, 2-cyanoethyl, propionyl or methoxymethyl or a pharmaceutically acceptable salt thereof.

12. A compound according to any of the claims 8-11 wherein

R^4 is hydrogen or $(CH_2)_m(CHR^9)$-(CH_2)p-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is -OH, -$NR^{14}R^{15}$ or C_{1-6}-alkoxy, wherein R^{14} and R^{15} are hydrogen or C_{1-6} alkyl and A is C=O or a pharmaceutically acceptable salt thereof.

13. A compound according to any of the claims 8-12 selected from the following:

(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,

{8-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester,

[8-(3-Cyano-3,3-diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(4-Nitro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[4-Oxo-1-phenyl-8-(3-phenyl-propyl)-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[4-Oxo-8-(3-phenoxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[4-Oxo-8-(4-phenoxy-butyl)-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

{8-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester,

(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,

{8-[2-(4-Fluoro-phenoxy)-ethyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl}-acetic acid methyl ester,

[8-(6,7-Dimethoxy-2-oxo-2H-chromen-4-ylmethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(3-Cyano-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

3-(3-Methoxycarbonylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-benzoic acid methyl ester,

[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

(8-Anthracen-9-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester ,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]pentanoic acid methylester,

N-(2-Guanidino-ethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

3-(7-Amino-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

3-(1H-Imidazol-4-yl)-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-propionamide,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

5-Guanidino-2-(R)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

N-(3-Guanidino-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

3-(5-Amino-pentyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

N-(3-Amino-propyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

N-(2-Amino-ethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

N-[7-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-heptyl]-guanidine,

3-Ethyl-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-N-(tetrahydro-furan-2-ylmethyl)acetamide,

2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-N-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-acetamide,

6-Amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoic acid amide,

N-Carbamoylmethyl-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide,

2-(S)-[2-(8-Naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-phenyl-acetamide,

6-Amino-2-(S)-(2-{6-amino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-hexanoylamino}-acetylamino)-hexanoic acid amide,

5-Guanidino-2-(S)-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-pentanoic acid amide,

5-Guanidino-2-(S)-(2-{2-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-acetylamino}-acetylamino)-pentanoic acid amide,

(4-Oxo-8-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid methyl ester,

[8-(2-Naphthalen-1-yl-ethyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(4-Bromo-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

[8-(3,4-Dichloro-benzyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester,

5-Guanidino-2-(S)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide,

5-Guanidino-2-(R)-[2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetylamino]-pentanoic acid amide or

3-(7-Amino-heptyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

14. A pharmaceutical composition comprising as active component a compound according to any of the claims 8-13 together with a pharmaceutical acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition suitable for use in the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances comprising an amount of compound according to any of the claims 8-13 together with a pharmaceutical carrier or diluent.

16. A pharmaceutical composition according to any of the claims 14 or 15 wherein it is in a form of an oral dosage unit or a form suitable for oral, nasal, transdermal, pulmonal parenteral dosage unit containing 0.1 to about 1000 mg per patient per day.

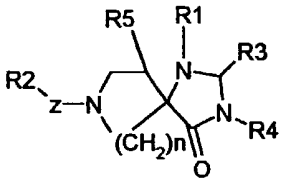
17. Use of a compound according to any of the claims 8-13 for the preparation of a medicament for treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances.

18. Use of a compound according to any of the claims 8-13 for the preparation of a medicament for treatment of vasomotor disturbances, especially hot flushes.

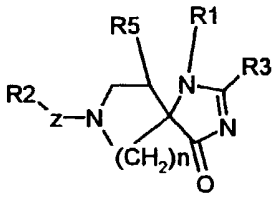
19. A method of treating hot flushes in a subject in need of such treatment comprising the step of administering to said object an amount of a compound according to any of the claims 8-13which is effective for the alleviation of such ailment.

20. A method of treating hot flushes in a subject in need of such treatment comprising the step of administering to said object an amount of a compound according to any of the claims 8-13 which is effective for the alleviation of such ailment in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

21. Use of a compound of the general formula



(Ia) or



(Ib)

wherein

R^1 is phenyl, arylalkyl or thienyl, optionally substituted with one or more of halogene, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^8 wherein R^6 and R^8 independently are hydrogen or C_{1-6}-alkyl, or R^1 is C_{1-6}-alkyl;

R^2 is

phenyl, phenoxy, benzodioxinyl, cyanodiphenylmethyl, aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, coumarinyl, said groups may be substituted with one or more of halogen, cyano, nitro,

trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, $C(O)R^7$, wherein R^7 is -OH, C_{1-6}-alkoxy or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} independently are hydrogen or C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is hydrogen or $(CH_2)_m$-(CHR^9)-$(CH_2)p$-AR^{11}, wherein m and p independently are 0-4 and R^9 is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl, R^{11} is C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, guanidino, an amino acid residue or a 2-4 peptidyl residue with a C-terminal group consisting of either OCH_3, or NH_2 ; R^{11} can also be a group $NR^{14}R^{15}$ wherein R^{14} and R^{15} independently are hydrogen, C_{1-6} alkyl, $(CH_2)qR^{16}$ where q can be 0 to 6 and R^{16} can be a C3-C7 membered cycloalkyl ring, an optionally substituted aromatic or heteroaromatic ring, an aliphatic ring containing one or more heteroatoms, an alkoxy or aryloxy group, an amino or a guanidino group; A is $-CH_2$ or -C=O; provided that when R^{11} is an amino acid or peptidyl residue, then A is a -C=O group;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or arylalkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene;

n is 1 or 2

or a pharmaceutically acceptable salt thereof for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence, vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes and/or for alleviating symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00266

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/10, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1043141 A (N.V. RESEARCH LABORATORIUM), 21 Sept 1966 (21.09.66), claim 11 --	9-18
X	Chemical Abstracts, Volume 81, No 5, 5 August 1974 (05.08.74), (Columbus, Ohio, USA), page 435, THE ABSTRACT No 25674h, JP, 7401573 A,, (Sasajima, Kikuo et al) 8 January 1974 (08.01.74), reg. no. 53164-94-6 --	9-18
X	Chemical Abstracts, Volume 78, No 9, 5 March 1973 (05.03.73), (Columbus, Ohio, USA), page 523, THE ABSTRACT No 58426v, JP, 7238971 A,, (Yamamoto, Hisao et al) 6 December 1972 (06.12.72), Compound II --	9-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1999	23 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00266

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3723441 A (CARL KAISER ET AL), 27 March 1973 (27.03.73), example 3 and 8	9-18
X	GB 1547597 A (BERTHOLD RICHARD VOGT ET AL), 20 June 1979 (20.06.79)	9-18
X	Chemical Abstracts, Volume 126, No 24, 16 June 1997 (16.06.97), (Columbus, Ohio, USA), Dukic, Sladjana et al, "Synthesis and dopaminergic properties of 3- and 4-substituted 1-(2-(5-(1H-benzimidazole-2-thione))ethyl)-piperidines and related compounds", page 73, THE ABSTRACT No 312189g, Arch. Pharm. 1997, 330 (1/2), 25-28, reg.no. 189209-03-8	9-18
X	Chemical Abstracts, Volume 70, No 17, 28 April 1969 (28.04.69), (Columbus, Ohio, USA), Lecolier, S., "LCAO method applied to the determination and synthesis of anthracenes with neuroleptic activity", page 264, THE ABSTRACT No 77149h, Chim. Ther. 1968, 3 (3), 193-199, reg. no. 22682-90-2 and 22753-42-0	9-18
X	J. Org. Chem., Volume 44, No 26, 1979, Anthony E. Lanzilotti et al, "Steroselective Reduction of Some Indoles with Triethylsilane-Trifluoracetic Acid1", page 4809 - page 4813, compound 2g	9-18
A	US 3238216 A (PAUL ADRIAAN JAN JANSSEN), 1 March 1966 (01.03.66)	9-18
A	US 3923993 A (ALAN CORBIN), 2 December 1975 (02.12.75)	9-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00266

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3863011 A (ALAN CORBIN), 28 January 1975 (28.01.75) --	9-18
A	WO 9113622 A1 (BETH ISRAEL HOSPITAL ASSOCIATION), 19 Sept 1991 (19.09.91) --	9-18
A	WO 9312789 A1 (BETH ISRAEL HOSPITAL), 8 July 1993 (08.07.93) --	9-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00266

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-21
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☒ Claims Nos.: 1-8
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-8 do not clearly define the matter for which protection is sought. A meaningful search has therefore not been performed, c.f. Article 6.

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/DK 99/00266

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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JP 7238971 A	06/12/72	KR 125807 B	06/04/98
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		US 3712898 A	23/01/73
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		US 5574041 A	12/11/96
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		US 5639758 A	17/06/97
		US 5703088 A	30/12/97